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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Chiron Corporation				WHITEMAN, BRIAN A
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Emeryville, CA 94662-8097			1635	

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SAC

Office Action Summary	Application No.	Applicant(s)	
	09/610,313	BARNETT ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 3/29/04.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-40 and 43-51 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-40,43-51 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____ .
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ .	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
	6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> .

DETAILED ACTION

Final Rejection

Claims 1-40 and 43-51 are pending.

Applicants' traversal, the amendment to claims, the cancellation of claim 42 in paper filed on 3/29/04 is acknowledged and considered.

This application contains sequence disclosures that are encompassed by the definition for nucleotide sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements for Patent Applications Containing Nucleotide Sequence Disclosures.

The amino acid sequence on page 75, line 2 does not have a SEQ ID NO: and is not listed in the CRF.

Specification

The disclosure is objected to because of the following informalities: the status (e.g., pending, abandoned, patented US Patent No.) of US non-provisional applications listed in the cross-reference is missing.

The disclosure remains objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See page 74. Applicants are required to delete any embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-40 and 47 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-40 and 47 as best understood, are readable on a genus of a polynucleotide sequence encoding an HIV Pol polypeptide that elicits a Pol-specific immune response, and further wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32, wherein the genus of polynucleotide sequences is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of a polynucleotide sequence encoding a polypeptide including an immunogenic HIV Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32. The as-filed specification provides sufficient description of an immunogenic HIV Pol polypeptide set forth in SEQ ID NO: 30, 31, or 32. The specification does not define the term “an HIV pol polypeptide that elicits a Pol-specific immune response”. The specification defines an “immunological response” as humoral and/or cellular immune response (page 15) and the cellular immune response could include a response with CD4+ cells and/or CD8+ cells. The specification does not disclose which nucleotides are considered essential for eliciting a humoral and/or cellular immune response. For example, the specification does not disclose what peptides encoded by SEQ ID NOS: 30-32 contain a CTL epitope. The as-filed specification recites that the synthetic HIV Pol polynucleotides will be capable of higher protein production compared to wild-type HIV Pol polynucleotide sequences (page 36). The specification and the art of record teach that HIV Pol comprises the enzymes reverse transcriptase (RT) and integrase (INT). The specification states, “Because synthetic HIV-1 Pol expressed the functional enzymes reverse transcriptase (RT) and integrase (INT) (in addition to the structural proteins and protease), it may be helpful in some instances to inactivate RT and INT functions (page 73).” The claims recite a structure and a function (polynucleotide encodes an HIV Pol polypeptide that elicits a Pol-specific immune response) for the genus of polynucleotide sequences. However, one skilled

could envision a polynucleotide sequence that is at least 90% identical to the claimed SEQ ID NOs., but would be unable to determine based on the description in the specification if the sequence has a function that is considered part of the claimed genus of DNA molecules. Thus, in view of the reasons set forth above and the numerous sequences embraced by the genus, the specification does not disclose which activities correspond to the claimed genus of polynucleotides with 90% sequence identity to the claimed SEQ ID NOs..

It is apparent that on the basis of applicants' disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of polynucleotide sequences as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of polynucleotide sequences that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient for the specification to contemplate a genus of polynucleotide sequences to support the presently claimed invention directed to a genus of a polynucleotide sequence that encodes an HIV Pol polypeptide that elicits a Pol-specific immune response, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicants' effective filing date. Claiming a genus of polynucleotide sequences that must possess the biological properties as contemplated by

applicants' disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a polynucleotide sequence encodes an HIV Pol polypeptide that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's arguments filed 3/29/04 have been fully considered but they are not persuasive.

With respect to applicants' argument that Example 4 provides support for an HIV Pol polypeptide that elicits a Pol-specific immune response, the argument is not found persuasive because Example 4 contemplates in vivo immunogenicity of synthetic Pol, Gag, and Env expression cassettes and whether the cassettes elicit either a humoral immune response or a cellular immune response. In addition, Table 1 lists gag or env expression cassettes but does not list any expression cassettes containing pol. The example does not describe what amino acids of

HIV pol are required to elicit a Pol-specific immune response. In addition, the specification does not define the limitation “a Pol-specific immune response”. The specification does not disclose which nucleotides of the claimed sequences are considered essential for eliciting a humoral and/or cellular immune response. Thus, the as-filed specification does not provide sufficient description for the claimed genus of polynucleotide sequences.

Applicants argue that the function of the polypeptide encoded by the claimed genus of polynucleotides is now more clearly set forth as immunogenic function rather than all biological functions. See pages 7-8. The argument is not found persuasive because the claims still read on a genus of polynucleotides that encode an HIV Pol polypeptide that elicits a specific Pol immune response and including any biological function. As stated above, the specification and the art of record teach that HIV-1 Pol expresses the functional enzymes reverse transcriptase (RT) and integrase (INT) (in addition to the structural proteins and protease). In addition, the specification does not describe which amino acids of an enzyme; structural proteins and protease are required for an HIV Pol polypeptide to elicit a Pol-specific immune response.

Applicants argue that immunogenic regions of Pol were known and could be readily determined (See Parker et al., (1994) J. Immunol. 152:163-175 and Pogue et al. (1995) PNAS 92:8166-8170) and that a polypeptide that is used for its immunogenicity can tolerate a variety of substitutions and still induce a specific immune response. See pages 8-9. The argument is not found persuasive because neither Parker nor Pogue provide support for the claimed genus of polynucleotides. Parker teaches a scheme for ranking potential HLA-A2 binding peptide based on independent binding of individual side-chains using synthetic nonamer peptides. Parker does not teach that immunogenic regions of Pol were known at the time the invention was made. The

specification does not disclose using the scheme taught by Parker for determining which amino acids of an HIV pol polypeptide comprising of at least 819 amino acids of SEQ ID Nos: 30-32 are required for eliciting a Pol-specific immune response. Pogue studies whether amino-terminal alteration of HIV pol increase complex stability and in vitro immunogenicity using a nonamer peptide with a HIV-1 pol epitope. The specification does not disclose using peptides and the assay taught by Pogue for determining which amino acids of an HIV pol polypeptide comprising of at least 819 amino acids of SEQ ID Nos: 30-32 are required for eliciting a Pol-specific immune response. See MPEP 608.01(p). Neither Parker nor Pogue describe which nucleotides or amino acids are considered essential for an HIV pol polypeptide to elicit a cellular and/or a humoral immune response.

Furthermore, the assertion that “a polypeptide that is used for its immunogenicity can tolerate a variety of substitutions and still induce a specific immune response” by applicant is not provided by any evidence of record. See MPEP § 716.01(c).

With respect to applicants’ argument that the degree of homology of the functional peptide to other peptides is irrelevant because the percent homology are directed to polynucleotides not proteins (See page 9), the argument is not found persuasive because it would have been plain to a skilled artisan that the function is directed to proteins and not polynucleotides. In addition, applicants cite Pogue and Parker for support of the claimed genus of polynucleotides. Both articles are directed to peptides and not polynucleotides.

Applicants argue that, “The non-immunogenic functions of RT and Int are not relevant to pending case. As is well known in the field, biological functions of a polypeptide and immunogenic function are separable and moreover, immunogenic function is typically retained

even when the amino acid substitutions are made. See Parker and Pogue.” See page 9. The argument based on Parker and Pogue are not found persuasive for the reasons set forth above. In addition, applicants’ argument is not found persuasive because the claims still read on an HIV polypeptide with functional RT and Int activity or other functional structural proteins and protease.

With respect to applicants’ argument that in view of Example 14 in the Patent Office’s “Synopsis of Application of Written Description Guidelines” the specification has written support (see pages 9-13). The argument is not found persuasive because the specification does not provide sufficient description of the claimed genus of polynucleotides. Pages cited for support of the claimed genus of sequences do not provide assays for determining whether a polypeptide elicits a Pol specific immune response. The specification does not lead one skilled in the art to using the methods and materials cited in the zur Megede post-filing reference. See MPEP 608.01(p). In addition, the zur Megede reference does not disclose which amino acids or nucleotides of SEQ ID NOs: 30-32 are considered essential for eliciting a cellular and/or a humoral immune response.

In addition, Example 14 in the Patent Office’s “Synopsis of Application of Written Description Guidelines” is part of training material and is not cited in the MPEP for determining whether a rejection under 112 first paragraph written description applies to a claimed invention. “The Guidelines do not constitute substantive rulemaking and hence do not have the force and effect of law. They are designed to assist Office personnel in analyzing claimed subject matter for compliance with substantive law. Rejections will be based upon the substantive law, and it is

these rejections, which are appealable. Consequently, any perceived failure by Office personnel to follow these Guidelines is neither appealable nor petitionable..” See MPEP 2163.

Furthermore, in view of the arguments on pages 9-12, it appears that applicants argue protein homology is relevant to the claimed invention (See pages 10-12) and not relevant to the claimed invention. Applicants argue that the protein in Example 14 is relevant to the claimed invention and applicants also argue that the degree of homology of the functional peptide to other peptides is irrelevant to the instant written description inquiry (page 9). Thus, it is not clear what position applicants are arguing with respect to protein homology.

With respect to applicants’ argument that the cited cases are not relevant. See pages 13-14. The argument is not found persuasive because as pointed by applicants both cases are directed to whether possession of a species can describe possession of a genus. This is the case here.

With respect to University of California v. Eli Lilly and Co. (CA FC) 43 USPQ2d 1398, the claimed genus of polynucleotides reads on a polynucleotide encoding an HIV pol polypeptide that elicits a Pol-specific immune response and retains any HIV pol activity. The claimed genus of polynucleotides are not described by general language of patent's written description supported only by specific nucleotide sequence of SEQ ID NO: 30-32. The claimed genus reads on wild type and synthetic HIV pol encoding polynucleotides. In view of the lack of description in the specification for which nucleotides constitute synthetic HIV polynucleotides and not wild-type HIV-pol polynucleotides, one skilled in the art would not be able to distinguish if a polynucleotide sequence was from a wild-type strain of HIV or from a synthetic HIV polynucleotide sequence. The specification does not provide written description of the claimed

genus of HIV pol encoding polynucleotides, wherein the HIV pol elicits a specific immune response. The specification does not include examples providing process for obtaining a claimed genus of HIV-pol encoding polynucleotides, and does not describe polypeptides that polynucleotides encode and provides no information, such as sequence information indicating which nucleotides constitute synthetic HIV polynucleotide and not a wild-type HIV-pol polynucleotide, pertaining to that polynucleotide's relevant structure or physical characteristics. description which renders claimed invention obvious is not sufficient to satisfy written description requirement of that invention, since claim to specific DNA is not made obvious by mere knowledge of desired protein sequence and methods for generating DNA that encodes that protein, and since description that does not render claimed invention obvious therefore does not sufficiently describe that invention for purposes of 35 USC 112.

With respect to See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993), the specification contains statements that claimed genus of polynucleotides is part of invention, and reference to potential method for isolating sequence, does not satisfy written description requirement of 35 USC 112, since specification does not describe DNA itself, nor even demonstrate that disclosed method would actually produce DNA in question, and since application therefore does not demonstrate that inventor had possession of claimed DNA.

Claims 1-40 and 47 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression cassette comprising the polynucleotide sequence set forth in SEQ ID NOs: 30, 31, or 32, does not reasonably provide enablement for a polynucleotide sequence encoding an HIV Pol polypeptide that elicits a Pol-specific immune

response, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention lies in the field of producing a composition comprising an expression cassette comprising a nucleotide sequence encoding an HIV Pol polypeptide, wherein the polynucleotide sequences has at least 90% sequence identity to the sequence set forth in SEQ ID NOs: 30-32 and using the composition for generating an immune response in a subject.

The applicants contemplate: 1) Expression assays for the synthetic coding region of Pol, Env, and Gag-protease expression cassettes; 2) In vivo immunogenicity of Gag, Pol, and Env expression cassettes using plasmid DNA carrying the synthetic Gag, Pol, and Env expression cassette; 3) DNA immunization of non-human primates by administering intradermally, mucosally, bilaterally, intramuscularly into the quadriceps using various doses of a synthetic Pol, Env, and Gag-containing plasmid; 4) In vitro expression of recombinant alphavirus vectors or plasmid containing the synthetic Gag, Pol, and Env expression cassette; 5) In vivo immunogenicity of recombinant Sindbis replicon vectors containing Gag, Env, and Pol expression cassettes in mice by using intramuscular and subcutaneous routes.

The specification further recites that these experiments will exhibit increased potency for induction of cytotoxic T-lymphocytes (CTL) response and humoral immune response by using the Gag, Pol, and Env expression cassettes.

The specification recites, "Because synthetic HIV-1 Pol expressed the functional enzymes reverse transcriptase (RT) and integrase (INT) (in addition to the structural proteins and protease), it may be helpful in some instances to inactivate RT and INT functions (page 73)."

The broadest claims read on a polynucleotide sequence encoding an HIV pol polypeptide that elicits a specific Pol immune response (humoral and/or cellular) and is functional (maintains a functional Int, RT, protease, etc.) and is at least 90% sequence identity to the sequence presented in SEQ ID NO: 30-32. The as-filed specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use a sequence having at least 90% identity to any of the sequences presented as SEQ ID NO: 30, 31, or 32 other than the sequences themselves. The claimed invention embraces polynucleotide sequences encoding an HIV Pol that elicits a Pol-specific immune response and has RT and INT activity, RT and/or INT activity and has other structural proteins and protease. The specification recites that HIV Pol comprises the enzymes reverse transcriptase (RT) and integrase (INT). The specification provides no guidance as to which (if any) of the amino acids may be changed while RT, INT, structural protein(s), protease activity are retained. The number of nucleotides in each SEQ ID NO: is at least 2457 nucleotides and thus at least 819 amino acids is encoded by each nucleotide sequence set forth in SEQ ID NOs: 30-32. The total number of 819 amino acid peptides is 1.85×10^{66} . The number of single amino acid substitutions is 15,561. The number of two amino acid substitutions is over 242,000,000. It is known for nucleic acids as well as proteins, for example,

that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The specification does not provide sufficient guidance and/or factual evidence that it was routine to substitute or delete at least 240 nucleotides of a 2,400 nucleotide sequence and determine which nucleotide sequences meet the functional limitation of the claims. The effects of these changes is largely unpredictable as to which ones have a significant effect versus not. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Baker et al., *Science*, 294:pages 93-96, 2001); Attwood, T (*Science*, vol. 290, no. 5491, pp. 471-473, 2000); Gerhold et al., (*BioEssays*, vol. 18, no. 12, pp. 973-981, 1996); Russell et al., *Journal of Molecular Biology*, vol. 244, pp 332-350, 1994); and Wells et al., *Journal of Leukocyte Biology*, vol. 61, no. 5, pp. 545-550, 1997). Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain immunogenic HIV Pol activity, and the fact that the relationship of the sequence of a peptide and its tertiary structure (e.g. its activity) are not well understood and are not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one skilled in the art in view of the prior art to arrive at other sequences that have at least 90% sequence identity to an Pol polypeptide that elicits a Pol-specific immune response encoded by SEQ ID NOs: 30-32 and still possess HIV Pol polypeptide activity. Since it would require undue experimentation to

identify other polypeptides that elicit a Pol specific immune response and retain the properties of a wild type HIV pol polypeptide, it certainly would require undue experimentation to make their corresponding DNA, and therefore, the entire scope of the claimed invention.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable making and using an expression cassette comprising the polynucleotide sequence set forth in SEQ ID NOs: 30, 31, or 32, does not reasonably provide enablement for a polynucleotide sequence encoding an HIV polypeptide that elicits a HIV Pol specific immune response, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the In Re Wands Factors including the lack of guidance in the application's disclosure, the unpredictability of producing nucleotide sequences encoding an HIV Pol polypeptide that elicits a Pol-specific immune response with 90% sequence identity to the claimed SEQ ID NOs.

Applicant's arguments filed 3/29/04 have been fully considered but they are not persuasive. In view of the In Re Wands Factors, the as-filed specification does not provide sufficient guidance for one skilled in the art to practice the full scope of the claimed invention.

With respect to applicants' arguments that non-immunogenic activities are irrelevant because of the amendment to the claims to recite an HIV pol polypeptide that elicits a Pol-specific immune response, the argument is not found persuasive because the claims still read on an HIV pol polypeptide with non-immunogenic activities (such as enzyme activities). The

amendment does not exclude the claim from embracing an HIV pol polypeptide with enzymatic activity of RT and Int or other structural proteins or protease. In addition, the specification does not define the limitation "HIV Pol polypeptide elicits a Pol-specific immune response". The claimed genus of nucleotide sequences embraces an HIV pol polypeptide that elicits a humoral and/or cellular immune response and the specification does not provide sufficient guidance and/or factual evidence for what nucleotides or amino acids are considered essential to practice the full scope of the claimed invention. Applicants cite Example 4 for support of the claimed genus of nucleotide sequences and Example 4 is a prophetic example. In view of the prophetic example cited for support in the specification, one skilled in the art would have to make a polynucleotide sequence, determine if it has 90% sequence identity to SEQ ID NOs: 30-32, then determine which nucleotides or amino acids are considered essential for eliciting a humoral and/or cellular immune response. For example, the specification does not teach what peptides encoded by SEQ ID NOs: 30-32 contain a CTL epitope. The specification must be enabling as of the filing date. See MPEP 2164.05(a). The art of record, at the time the application was filed, is absent for making and testing a genus of polynucleotide sequences encoding an HIV pol polypeptide and determining what nucleotides or amino acids are considered essential for eliciting a humoral and/or cellular immune response. Given the above analysis of the In Re Wands factors, which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have conducted undue and excessive experimentation in order to practice the full scope of the claimed invention.

With respect to applicants' argument that the degree of homology of the functional peptide to other peptides is irrelevant because the percent homology are directed to

polynucleotides not proteins (See page 15), the argument is not found persuasive because it would have been plain to a skilled artisan that the function is directed to proteins and not polynucleotides. Furthermore, applicants based some of their argument on the assertion that methods of making and testing polypeptides from these structures are not undue experimentation.

Applicants argue that the specification as filed provides clear examples of substitutions/deletions as claimed, namely SEQ ID NOS: 30-32 and the additional evidence (Declaration of record, Parker and Pogue) of record fully supports the specification's teaching that the Pol polypeptides were well characterized in terms of immunogenicity. In addition, applicants remind the examiner that the specification does not need to teach in detail that which is conventional or well known. See pages 16-17. The argument is not found persuasive because the Declaration of record, Parker or Pogue do not provide support for the claimed genus of polynucleotides. The declaration does not address making and using a genus of polynucleotide sequences encoding an HIV pol polypeptide that elicits a cellular and/or a humoral immune response. Parker teaches a scheme for ranking potential HLA-A2 binding peptide based on independent binding of individual side-chains using synthetic nonamer peptides. Parker does not teach that immunogenic regions for eliciting a cellular and/or humoral immune response of an HIV Pol polypeptide based on SEQ ID NOS: 30-32 were known at the time the invention was made. The specification does not teach using the scheme taught by Parker for determining which amino acids of an HIV pol polypeptide comprising of at least 819 amino acids of SEQ ID Nos: 30-32 are required for eliciting a Pol-specific immune response. Pogue studies whether amino-terminal alteration of HIV pol increase complex stability and in vitro immunogenicity using a

nonamer peptide with a HIV-1 pol epitope. The specification does not teach using peptides and the assay taught by Pogue for determining which amino acids of an HIV pol polypeptide comprising of at least 819 amino acids of SEQ ID Nos: 30-32 are required for eliciting a Pol-specific immune response. See MPEP 608.01(p).

In addition, the as-filed specification does not provide sufficient guidance and/or factual evidence for making and using the claimed genus of polynucleotide sequences and does not provide support that it was routine to make and use the claimed genus of polynucleotide sequences. Example 4 contemplates in vivo immunogenicity of synthetic Pol, Gag, and Env expression cassettes and whether the cassettes elicit either a humoral immune response or a cellular immune response. In addition, Table 1 lists gag or env expression cassettes but does not list any expression cassette containing pol. The example does not describe to one skilled in the art what nucleotides or amino acids of HIV pol are required to elicit a Pol-specific immune response. Thus, nothing in specification provides support that Pol polypeptides that elicit a Pol-specific immune response were well characterized in terms of immunogenicity and that immunogenicity may be retained when amino acid substitutions are made.

With respect to applicants' argument that the fact that those working in the field would have understood how to test for immunogenicity and the specification sets forth in detail how to test for antigen-specific immune responses (e.g., Example 4) does not support a finding of nonenablement, the argument is not found persuasive because the specification must be enabling as of the filing date. See MPEP 2164.05(a). As stated above, the claims still embrace functional HIV polypeptides and the specification does not teach one skilled in the art how to make and use the claimed genus of polynucleotide sequences. In addition, the specification does not provide

sufficient guidance and/or factual evidence for how one skilled in the art can reasonably extrapolate from making SEQ ID NO: 30-32 to making a genus of polynucleotide sequences that encode an HIV Pol polypeptides that elicit a Pol-specific immune response without undue and excessive experimentation.

With respect to applicants argument that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claimed non-enabled (See MPEP 2164.08(b)) and the claim language itself excludes inoperative embodiments, the argument is not found persuasive because the fact that the claims exclude inoperative embodiments is irrelevant because 112 first paragraph (enablement) requires that the specification teach one skilled in the art how to make the claimed invention and the specification lacks sufficient guidance for one skilled to make the claimed genus of polynucleotide sequences as broadly claimed and determine which polynucleotide are considered operable/inoperable without undue and excessive experimentation. In addition, the claims still embrace functional HIV polypeptides (e.g., retaining RT, Int, protease activity, etc.) and the as-filed specification does not teach one skilled in the art how to make and use the claimed genus of polynucleotide sequences. The specification fails to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen at least 1.85×10^{66} amino acid peptide for peptides that meet or do not meet the limitations set forth in the claims. The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a

“plan” or “invitation” for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the as-filed specification provides no more than a plan or invitation for experimentation in view of the art of record exemplifying the unpredictability of making and using any polynucleotide sequence with 90% sequence identity to SEQ ID NOs: 30-32 that encodes an HIV pol polypeptide that elicits a Pol-specific immune response, for those skilled in the art to experiment with polynucleotide sequences with 90% sequence identity to SEQ ID NOs: 30-32 to produce a genus of claimed polynucleotide sequences as intended by the as-filed specification at the time the invention was made. In addition, In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states:

Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements, while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

With respect to applicants’ arguments that the newly cited references all relate to difficulties in predicting the function of an unknown and uncharacterized polypeptide encoded by a similarly uncharacterized polynucleotide and do not establish unpredictability, the argument is not found persuasive because the specification fails to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen at least 1.85×10^{66} amino

acid peptide for peptides that meet or do not meet the limitations set forth in the claims. The claimed invention embraces unknown and uncharacterized polypeptides encoded by uncharacterized polynucleotides and the cited references teach the unpredictability of the relationship between sequence and function.

Furthermore, with respect to applicants' argument that the pertinent issue in the pending case is whether the specification teaches how to make and use polynucleotides having the requisite homology to the claimed reference sequence that encodes a pol polypeptide that elicits an pol-specific immune response and that this is an entire different question than whether or nor the function of amino acid sequences encoded by polynucleotides identified by genomic methods can be predicted based on linear sequence alone, as discussed in the cited documents, the argument is not found persuasive because in view of the lack of guidance provided by the specification for what nucleotides or amino acids are considered essential for eliciting a cellular and/or humoral immune response, one skilled in the art would have to make a polynucleotide sequence, determine if the sequence has 90% sequence identity to SEQ ID NOs: 30-32, then determine which nucleotides or amino acids are considered essential for eliciting a humoral and/or cellular immune response. The specification fails to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen at least 1.85×10^{66} amino acid peptide for HIV pol peptides that meet or do not meet the limitations set forth in the claims. The specification must be enabling as of the filing date. See MPEP 2164.05(a).

Applicants argue that the Enzo case cited in the office action is not relevant because the Enzo's facts are completely different than those in the case at hand and Enzo does not relate to the question of enablement of sequences; Enzo actually supports Applicants' arguments that their

specification fully enables claims that encompass only sequences exhibiting the requisite high level of homology to a reference sequence and recited function. The examiner acknowledged that Enzo is directed to the use of a genus of DNA constructs in cells. However, the principle of the case is directed to the breadth of enablement was not commensurate in scope with the claims and using the In Re Wands Factors to show that the full scope of the claimed invention was not enabled. This is the case here. The amount of direction presented and the number of working examples provided in the specification were very narrow compared to the wide breadth of the claims at issue (at least 1.85×10^{66} amino acid peptide are embraced by only polypeptide encoded by a claimed SEQ ID NO), predicting function of an amino acid based on its nucleotides sequence was unpredictable, and the amount of experimentation required to adapt the practice of is excessive and undue (screen at least 1.85×10^{66} amino acid peptide for peptides that meet or do not meet the limitations set forth in the claims).

Furthermore, the request by applicants for an affidavit from the examiner to support personal knowledge that results relating to subtype B are inapplicable to analogous constructs from subtype C strains for that of Dr. Donnelly (see page 21) is unclear because the applicants do not describe where the examiner substitutes personally knowledge for that of Dr. Donnelly.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 43-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 43-46 recite the limitation "The method of claim 42" in line 1. There is insufficient antecedent basis for this limitation in the claim. The claims depend on a cancelled claim (claim 42).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 48-51 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 71, 72, and 91 of co-pending Application No. 09/899,575 (SEQ ID NO: 30). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims from both applications recite an expression cassette comprising a polynucleotide sequence encoding a polypeptide including an immunogenic HIV Pol polypeptide. SEQ ID NO: 30 in the instant application is 100% identical to SEQ ID NO: 30 in application '575.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' argument that the applicants request the provisional double patenting rejection be held in abeyance as at allowable claims does not overcome the rejection and the

rejection remains. The “provisional” double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that “provisional” double patenting rejection is the only rejection remaining in one of the applications. See MPEP 804 I B.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764.

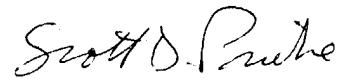
Art Unit: 1635

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicants attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- 2. This application does not contain, as a separate part of the disclosure on paper copy, a Sequence Listing as required by 37 C.F.R. 1.821(c).
- 3. A copy of the ASequence Listing in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- 4. A copy of the ASequence Listing in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up ARaw Sequence Listing.
- 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- 6. The paper copy of the ASequence Listing is not the same as the computer readable form of the ASequence Listing as required by 37 C.F.R. 1.821(e).
- 7. Other: An amino acid sequence on page 75, but there is no SEQ ID NO: and it is missing from the CRF.

Applicant Must Provide:

- An initial or substitute computer readable form (CRF) copy of the ASequence Listing.
- An initial or substitute paper copy of the ASequence Listing, as well as an amendment directing its entry into the specification.
- A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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